

REMARKS

Claims 6, 8, 9, 19, and 21-24 are pending and under examination.

Independent claims 8 and 22 have each been amended to include the language “wherein the differentiating stem cell, the differentiating stem cell tissue, and the differentiating stem cell nucleus are not differentiated.” Claim 22 has also been amended to include the language “wherein the differentiating embryonic stem cell and the differentiating trophoblast stem cell are not differentiated.” Those amendments merely expressly state what was previously implied. Accordingly, no new matter has been added.

I. Rejection of Claims 6, 8, 9, 19, and 21-24 Under 35 U.S.C. § 112, First Paragraph

The Office rejected claims 6, 8, 9, 19, and 21-24 under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement. Office Action at page 2, item no. 2. The Office alleges that “[t]he claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.” *Id.* at pages 2-3. Specifically, the Examiner bases the rejection on the alleged lack of express support for “differentiating stem cell,” “differentiating stem cell tissue,” and “differentiating stem cell nucleus.” *Id.* at page 3.

Applicants respectfully traverse the rejection. While the Office acknowledges that the specification at page 13, lines 21-26 discusses determining “the degree of stem cells,” the Office asserts that “it is unclear what is meant by degree of stem cells.” *Id.* at page 3. The Office also alleges that “one degree of a stem cell may be a fully differentiated cells, and the degree of a stem cell is not limited to a differentiating stem cell.” *Id.*

Solely to expedite prosecution, and without acquiescing to the Office's contentions, Applicants have amended independent claims 8 and 22 to include the language "wherein the differentiating stem cell, the differentiating stem cell tissue, and the differentiating stem cell nucleus are not differentiated." Claim 22 has also similarly been amended to include the language "wherein the differentiating embryonic stem cell and the differentiating trophoblast stem cell are not differentiated." Those amendments merely make express what was previously implied, and thus, add no new matter. Accordingly, "differentiating stem cell," differentiating stem cell tissue," and "differentiating stem cell nucleus" are clear and do not include "fully differentiated cells."

Moreover, the Office acknowledges that "the specification provides example[s] of differentiated cells such as brain or intestine, or undifferentiated stem cells." *Id.* Applicants assert that, at the time the application was filed, one skilled in the art would have readily understood that as stem cells progress from undifferentiated stem cells to differentiated cells, they are necessarily "differentiating." As evidence of the knowledge of one skilled in the art at the time the application was filed, Applicants include copies of Thomson et al., Proc. Natl. Acad. Sci. USA 92:7844-7848 (1995) ("Thomson") and Potocnik et al., Proc. Natl. Acad. Sci. USA 94:10295-10300 (1997) ("Potocnik"), both of which were published well before the filing date of the present application and also well before the earliest application for which benefit of priority is claimed.

Thomson discusses isolation of a primate embryonic stem cell line and states that "[e]mbryonic stem (ES) cells . . . are undifferentiated, immortal cells capable of *differentiating* into derivatives of all three embryonic germ layers." Thomson at page 7844, left col. (emphasis added). Potocnik discusses ES cell differentiation *in vitro*, and notes that "[i]nitial reports on

differentiating ES cells described the presence of hematopoietic cytokines and their respective receptors and of myeloid and erythroid progenitors.” Potochnik at page 10295, left col. (emphasis added). Accordingly, as evidenced by Thomson and Potochnik and the usage of “differentiating” in those publications, one skilled in the art would recognize the express description of undifferentiated stem cells and differentiated cells in the specification as necessarily supporting “differentiating stem cell,” “differentiating stem cell tissue,” and “differentiating stem cell nucleus” according to the claimed methods, sufficient to show implicit support for these terms.

Accordingly, Applicants assert that the specification provides written description for “differentiating stem cell,” “differentiating stem cell tissue,” and “differentiating stem cell nucleus” according to the claimed methods. Applicants further assert, as discussed above, that the recitation of “wherein the differentiating stem cell, the differentiating stem cell tissue, and the differentiating stem cell nucleus are not differentiated,” and “wherein the differentiating embryonic stem cell and the differentiating trophoblast stem cell are not differentiated,” are clear and that the claimed methods do not include “fully differentiated cells.” Thus, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 6, 8, 9, 19, and 21-24 under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement.

II. Rejection of Claims 8, 19, 21 and 22 Under 35 U.S.C. § 103(a)

The Office reinstated the rejection of claims 8, 19, 21, and 22 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Olek et al. (U.S. Patent No. 6,214,556 B1) (Olek”) in view of Labosky et al., Development 120:3197-3204 (1994) (“Labosky”). Office Action at page 4, item no. 3. Applicants respectfully traverse the rejection.

As an initial matter, Applicants respectfully point out that the Office had previously rejected those claims in view of the same documents making essentially the same allegations. See Office Action mailed on March 7, 2006, at pages 3-5. Applicants responded fully to those rejections in the Amendment and Response dated June 6, 2006, at pages 5-9. The Office considered those arguments and withdrew the rejection stating “[a]pplicants’ arguments, filed June 6, 2006, have been fully considered and they are deemed to be persuasive.” Office Action mailed on August 18, 2006, at page 2, item no. 1. In the present Office Action, the Office has not indicated any basis for reconsidering the Applicants’ prior arguments and has provided no justification for the reinstatement of the rejection in view of those arguments. Accordingly, Applicants respectfully request withdrawal of the rejection of claims 8, 19, 21, and 22 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Olek in view of Labosky.

While Applicants believe that the rejection should be withdrawn for at least the reasons stated above, they nevertheless respond fully to the Office’s present allegations below. The Office alleges that the “[t]he instant claims are drawn to a method of identifying the differentiation state of a stem cell by comparing the methylation pattern of a stem cell to the methylation pattern of a cell of a known differentiation state.” Office Action at page 4. The Office further alleges that “Olek et al. teaches a generic method of identifying cell types as well as cell states or stages through the use of methylation fingerprint patterns.” *Id.* In addition, the Office alleges that

[Olek] teaches obtaining a DNA methylation pattern for a test cell . . . which comprises information the methylation of CpG at a plurality of gene regions . . . ; obtaining a reference pattern for a particular cell type . . . ‘comparing the test cell DNA methylation pattern with the reference pattern . . . ’ and matching the test cell DNA methylation pattern with a reference patter to determine the cell type.

Id. at pages 4-5 (citations omitted).

The Office acknowledges that Olek does not teach “determin[ing] the differentiation state of a stem cell, nor the instant claims as the[y] are specifically applied to differentiation states or where the differentiation state is undifferentiated as in claim 21.” *Id.* at page 5. However, the Office alleges that “Labosky et al. provide the methylation patterns of embryonic germ cell lines (undifferentiated cells), embryonic stem cell lines, and compare the patterns of methylation of the embryonic germ cell lines and the embryonic stem cell lines.” *Id.* The Office then concludes that “[o]ne of ordinary skill in the art at the time the invention was made would have combined the methods of Olek et al. with the patterns discovered by Labosky et al. to create a method of identifying stem cells” *Id.* In particular, the Office alleges that Labosky provides methylation patterns and that “one of ordinary skill in the art would be motivated to take the DNA methylation pattern [of] Labosky et al. and incorporate it into Olek et al.’s method in order to identify unknown cell samples.”

Applicants assert, as in the Amendment and Response dated June 6, 2006, that the combination of Olek and Labosky would not have rendered obvious any of claims 8, 19, 21, and 22. As provided in the M.P.E.P. at § 2141 at page 2100-116, and in the “Examination Guidelines for Determining Obviousness in Light of the Supreme Court’s *KSR v. Teleflex Decision*,” 72 FR 57526-57535 (“Guidelines”) published on October 10, 2007, it is Office policy to follow *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966) in the consideration and determination of obviousness under § 103. As stated in the M.P.E.P., *Graham* provides

four factual inquiries . . . as a background for determining obviousness [a]s follows:

- (A) Determining the scope and contents of the prior art;
- (B) Ascertaining the differences between the prior art and the claims in issue;
- (C) Resolving the level of ordinary skill in the pertinent art; and
- (D) Evaluating evidence of secondary considerations.

M.P.E.P. at § 2141 at page 2100-116. In addition, three basic criteria that must be met to establish a *prima facie* case of obviousness, the so-called “teaching-suggestion-motivation” test, continues to be recognized as “one of a number of valid rationales that could be used to determine obviousness.” Guidelines at 57528. The *prima facie* case of obviousness is as follows:

First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

See M.P.E.P. at § 2143 at page 2100-126.

Applicants assert, as in the Amendment and Response dated June 6, 2006, that neither Olek nor Labosky, alone or in combination, teach or suggest all the limitations of either independent claim 8 or independent claim 22. For example, neither of those documents, either alone or in combination, teach or suggest

obtaining a differentiation state-specific DNA methylation pattern for one or more cell, tissue, or nucleus of known differentiation state, wherein the one or more cell, tissue, or nucleus of known differentiation state is selected from a stem cell, a stem cell tissue, a stem cell nucleus, a differentiating stem cell, a differentiating stem cell tissue, and a differentiating stem cell nucleus, wherein the differentiating stem cell, the differentiating stem cell tissue, and the differentiating stem cell nucleus are not differentiated,

as recited in independent claim 8. Nor do either of those documents, either alone or in combination, teach or suggest

obtaining a cell-, tissue-, or nucleus-specific DNA methylation pattern for one or more known types of cell, tissue, or nucleus; wherein the one or more known types of cell, tissue, or nucleus is selected from undifferentiated embryonic stem cell, differentiating embryonic stem cell, undifferentiated trophoblast stem cell, and differentiating trophoblast stem cell, wherein the differentiating embryonic stem cell and the differentiating trophoblast stem cell are not differentiated,

as recited in independent claim 22.

In addition, as discussed in the Amendment and Response dated June 6, 2006, Labosky studied “the methylation state of the putative imprinting box of the maternally expressed insulin-like growth factor 2 receptor (*Igf2r*) gene . . . in different EG cell lines, . . . normal somatic cells and ES cells.” Labosky at page 3198. Labosky discusses certain results in Fig. 2. (p. 3201) and Table 3 (p. 3200). Labosky states that “[h]alf of the 8.5 days p.c. derived EG cell lines (9 out of 18) . . . [show a] pattern of methylation [that] is characteristic of somatic cells and 5 different pluripotent ES cell lines. . . . The remaining [EG] cell lines . . . have a different pattern of methylation. . . .” *Id.* at page 3200 (references to tables, figures, and named cell lines omitted). Since Labosky shows that the methylation pattern of half of the EG cell lines is “characteristic of somatic cells and 5 different pluripotent ES cell lines,” while the methylation pattern of the other half of EG cell lines is “different,” it clearly does not teach or suggest

obtaining a differentiation state-specific DNA methylation pattern for one or more cell, tissue, or nucleus of known differentiation state, wherein the one or more cell, tissue, or nucleus of known differentiation state is selected from a stem cell, a stem cell tissue, a stem cell nucleus, a differentiating stem cell, a differentiating stem cell tissue, and a differentiating stem cell nucleus, wherein the differentiating stem cell, the differentiating stem cell tissue, and the differentiating stem cell nucleus are not differentiated.

For at least the same reasons, Labosky et al. similarly does not teach or suggest

obtaining a cell-, tissue-, or nucleus-specific DNA methylation pattern for one or more known types of cell, tissue, or nucleus; wherein the one or more known types of cell, tissue, or nucleus is selected from undifferentiated embryonic stem cell, differentiating embryonic stem cell, undifferentiated trophoblast stem cell, and differentiating trophoblast stem cell, wherein the differentiating embryonic stem cell and the differentiating trophoblast stem cell are not differentiated.

Not only does Labosky fail to teach or suggest the claimed methods, it actually teaches away from them. For example, Labosky discusses that certain methylation patterns are shared between embryonic cells at two different stages of development (EG cells and ES cells) and somatic cells (terminally-differentiated fibroblasts). Labosky at page 3200. Thus, those results

demonstrate a methylation pattern that is neither “differentiation state-specific” nor “cell-, tissue-, or nucleus-specific.” As a further example, Labosky demonstrates that half of the EG cell lines have a certain methylation pattern, while the other half has a different methylation pattern. *Id.* Thus, EG cells do not have a methylation pattern that one skilled in the art would recognize as “differentiation state-specific” or “cell-, tissue-, or nucleus-specific.” Nowhere does Labosky teach or suggest such “differentiation state-specific” or “cell-, tissue-, or nucleus-specific” methylation patterns. Indeed, the results discussed above, as well as the demonstrated methylation heterogeneity and methylation instability of the EG cell lines (*see, e.g.*, Table 3, Figs. 2 and 3) teach away from the claimed “differentiation state-specific DNA methylation patterns” and the claimed “cell-, tissue-, or nucleus-specific DNA methylation patterns.”

Because Labosky teaches away from the claimed invention, as discussed above, one skilled in the art would have had no reason to combine Labosky with Olek. Moreover, based on the results of Labosky, one skilled in the art would not have had a reasonable expectation of success, nor would have predicted obtaining

a differentiation state-specific DNA methylation pattern for one or more cell, tissue, or nucleus of known differentiation state, wherein the one or more cell, tissue, or nucleus of known differentiation state is selected from a stem cell, a stem cell tissue, a stem cell nucleus, a differentiating stem cell, a differentiating stem cell tissue, and a differentiating stem cell nucleus, wherein the differentiating stem cell, the differentiating stem cell tissue, and the differentiating stem cell nucleus are not differentiated,

or

a cell-, tissue-, or nucleus-specific DNA methylation pattern for one or more known types of cell, tissue, or nucleus; wherein the one or more known types of cell, tissue, or nucleus is selected from undifferentiated embryonic stem cell, differentiating embryonic stem cell, undifferentiated trophoblast stem cell, and differentiating trophoblast stem cell, wherein the differentiating embryonic stem cell and the differentiating trophoblast stem cell are not differentiated,

as taught by the present inventors.

Thus, for at least these reasons, the Office has failed to establish that independent claims 8 and 22, as well as claims 19 and 21, which depend from claim 8, would have been obvious in view of Olek and/or Labosky. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 8, 19, 21, and 22 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Olek in view of Labosky.

III. Rejection of Claims 6, 9, and 23 Under 35 U.S.C. § 103(a)

The Office also reinstated the rejection of claims 6, 9, and 23 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Olek in view of Labosky, and further in view of Ohgane et al., Dev. Genetics 22:132-140 (1998) (“Ohgane”). Office Action at page 6, item no. 4. Applicants respectfully traverse the rejection.

Applicants have already addressed these claim rejections in view of these cited documents, similar to the situation discussed above concerning claims 8, 19, 21, and 22. *See* Office Action mailed on March 7, 2006, at pages 4-5, and Amendment and Response dated June 6, 2006, at pages 5-9. Just as discussed above, the Examiner considered Applicants’ arguments persuasive and withdrew the rejection. Office Action mailed on August 18, 2006, at page 2, item no. 1. Accordingly, Applicants respectfully request withdrawal of the rejection of claims 6, 9, and 23 under § 103(a) as allegedly being unpatentable over Olek in view of Labosky, and further in view of Ohgane.

While Applicants believe that the rejection should be withdrawn for at least the reasons stated above, they nevertheless respond fully to the Office’s present allegations below. The Office acknowledges that “neither Olek et al. and Labosky et al. teach finding patterns in at least 1,000 gene regions or using RLGS profiles.” Office Action at page 6. The Office contends that Ohgane discusses comparison of methylation patterns at 2900 sites of trophoblast giant cell DNA

with labyrinth zone and maternal kidney cells by use of the RLGS method. *Id.* The Office alleges that

[i]t would have been obvious at the time of the invention to incorporate the methods taught by Ohgane et al. with Olek et al. and Labosky et al. to gain the benefit being able to generate methylation patterns of a large numbers of genes in order to make that pattern more specific for the state of the cell. . . [O]ne of ordinary skill in the art seeking to create specific methylation pattern for a cell would use Ohgane et al.'s strategy of using a large number of genes with the method of Olek et al. to identify an unknown cell sample.

Id. at pages 6-7.

Claims 6 and 9 depend from claim 8, and thus include all of the elements of claim 8; and claim 23 depends from claim 22, and thus includes all of the elements of claim 22. Applicants discussed above that neither of independent claims 8 and 22 would have been obvious in view of Olek and/or Labosky. Accordingly, none of claims 6, 9, or 23 would have been obvious in view of Olek and/or Labosky. Ohgane does not cure the deficiencies of Olek and Labosky.

Ohgane is silent concerning

a differentiation state-specific DNA methylation pattern for one or more cell, tissue, or nucleus of known differentiation state, wherein the one or more cell, tissue, or nucleus of known differentiation state is selected from a stem cell, a stem cell tissue, a stem cell nucleus, a differentiating stem cell, a differentiating stem cell tissue, and a differentiating stem cell nucleus, wherein the differentiating stem cell, the differentiating stem cell tissue, and the differentiating stem cell nucleus are not differentiated,

according to the method of claim 8, and

a cell-, tissue-, or nucleus-specific DNA methylation pattern for one or more known types of cell, tissue, or nucleus; wherein the one or more known types of cell, tissue, or nucleus is selected from undifferentiated embryonic stem cell, differentiating embryonic stem cell, undifferentiated trophoblast stem cell, and differentiating trophoblast stem cell, wherein the differentiating embryonic stem cell and the differentiating trophoblast stem cell are not differentiated,

according to the method of claim 22. Therefore, one skilled in the art would have had no reason to combine Ohgane with Olek and/or Labosky. Furthermore, one skilled in the art would not

have been able to predict, or have had a reasonable expectation of success of the claimed methods at least for the reasons discussed above concerning the rejection of claims 8, 19, 21, and 22 in view of Olek and Labosky. Therefore, claims 6, 9, and 23 would not have been obvious in view of Olek and Labosky and further in view Ohgane. Thus, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 6, 9, and 23 under § 103(a) as allegedly being unpatentable over Olek and Labosky and further in view of Ohgane.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully assert that the application is in condition for allowance and request the timely issuance of a Notice of Allowance. If the Examiner does not consider the claims allowable, the undersigned requests that, prior to taking action, the Examiner call her at (650) 849-6749 to set up an interview.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

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